

COEXISTING PROSTATE CANCER FOUND AT THE TIME OF HOLMIUM LASER ENUCLEATION OF THE PROSTATE FOR BENIGN PROSTATIC HYPERPLASIA: PREDICTING ITS PRESENCE AND GRADE IN ANALYZED TISSUE

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Abstract

Objective: To determine the incidence of prostate cancer identified on holmium enucleation of the prostate (HoLEP) specimens and evaluate variables associated with prostate cancer identification.

Methods: All patients undergoing HoLEP between 1998 and 2013 were identified. Patients with a known history of prostate cancer were excluded. Multivariable logistic regression assessed variables associated with identification of prostate cancer on HoLEP specimens and Gleason 7 or higher prostate cancer among the malignant cases. Gleason grade was used as a proxy for disease severity. Each of the models was adjusted for age, preoperative PSA, and HoLEP specimen weight.

Results: The cohort was comprised of 1272 patients of whom 103 (8.1%) had prostate cancer identified. Prostate cancer cases had higher pre-HoLEP PSA ($p=0.06$) but lower HoLEP specimen weight ($p=0.01$). On multivariate logistic regression, age and preoperative PSA were associated with increased odds of prostate cancer being present ($p<0.01$ each) while increasing HoLEP specimen weight was associated with decreased odds of prostate cancer ($p<0.001$). Men older than 80 had 20% predicted probability of being diagnosed with prostate cancer. Seventy-eight percent of prostate cancer cases were Gleason 6 or less. Pre-HoLEP PSA was associated with increased adjusted odds of intermediate or high grade prostate cancer.

Conclusion: Prostate cancer identified by HoLEP is not uncommon but is generally low risk disease. Older patients with smaller prostate glands have the highest odds of prostate cancer identification.

Introduction

Benign prostatic hyperplasia (BPH) affects a significant proportion of men in the United States with 70% of men in their seventh decade demonstrating histologic evidence and 40% displaying moderate to severe urinary symptoms¹. Many will undergo active intervention with 912 per 100,000 men in the US undergoing a BPH procedure in 2008². While TURP remains the most common active intervention for BPH^{2,3}, a well-established alternative is holmium laser enucleation of the prostate (HoLEP). HoLEP, initially described in 1996, reliably provides a more complete resection when compared with TURP, especially for large glands, with a superior safety profile^{4,5}. As with TURP, HoLEP is a procedure that provides tissue for pathologic analysis.

Before the adoption of prostate specific antigen (PSA) screening, almost 20% of prostate cancer was diagnosed from TURP⁶⁻⁸. However, since the introduction of PSA screening, this rate has declined significantly to 6-8%⁸. Previous studies have demonstrated that up to 12% of men undergoing HoLEP will be found to have prostate cancer in their analyzed tissue^{9,10}. Most studies have suggested that prostate cancer identified on HoLEP is generally indolent but some men may ultimately require subsequent treatment of their prostate cancer. In our experience, post-HoLEP robot-assisted radical prostatectomy, although feasible with encouraging oncologic outcomes, is a more challenging operation associated with longer functional recovery times compared to historical controls¹¹. Thus, identifying men at increased risk for clinically significant prostate cancer is an important consideration in managing patients with BPH disease who are considering enucleation surgery.

Our primary objective was to identify the incidence of prostate cancer identified by HoLEP in men with no history of prostate cancer. Additionally, we sought to determine preoperative variables that can be used to predict the presence of prostate

cancer in men undergoing HoLEP and to examine the burden of prostate cancer disease in this at risk patient population.

Methods

A retrospective analysis of patients who underwent HoLEP at IU Health Methodist Hospital between 1998 and 2013 was performed. Patients with a prior history of prostate cancer diagnosis were eliminated from the analysis (n=34). Pre-operative data including age, PSA, transrectal ultrasonography (TRUS) of prostatic volume, and PSA density were collected. Additionally, post-operative data including final specimen weight and pathological tissue findings were recorded. Patients without pre-operative PSA were eliminated (n=221). Patients with elevated PSAs (at the referring urologist's discretion) had negative pre-operative prostate biopsies. Prostate volume as assessed by TRUS was identified for 76% of patients. PSA density was calculated from preoperative PSA and TRUS prostate volume and was available for 75% of patients. We acknowledge that the likelihood of identifying prostate cancer may vary between patients with a history of TRUS biopsy and those without; however, to the extent of our documentation, the detection of cancer at the time of HoLEP did not vary between patient populations (p=0.314).

HoLEP was performed in similar fashion to our previously described technique¹². Briefly, using a 550 micron end firing laser fiber through a 28 Fr continuous flow resectoscope, the transition zone of the prostate was completely enucleated. Next, using a Lumenis morcellator (Yokneam, Israel), morcellation was completed removing the excised tissue from the bladder and prostatic fossa. The entire HoLEP specimen was submitted for pathologic analysis by dedicated genitourinary pathologists.

The relationship between pre- and post-operative variables and identification of the presence of prostate cancer was assessed using univariate and multivariate logistic

regression models. A separate multivariate logistic regression model was performed on patients with prostate cancer to evaluate the relationship between preoperative variables and Gleason 7 or higher disease. The variables chosen for univariate analyses were age, pre-operative PSA, pre-operative TRUS volume, final weight of prostate specimen from HoLEP, and percent of prostate resected. For multivariate analyses, only age, pre-operative PSA, and the HoLEP specimen weight were included. As TRUS volume was not available for 24% of patients, we chose to use HoLEP specimen weight in the analysis as it was available for 97% of patients. Patients with missing data were excluded from the regression analyses. All statistical analyses were performed using Stata version 12.1 (Stata Corp. LP, College Station, TX). In all tests, a two-tailed significance level of $p < 0.05$ was used. Institutional Review Board approval was granted for the conduct of this study.

Results

Patient pre-operative and post-operative characteristics are demonstrated in Table 1. A total of 1272 patients undergoing HoLEP between 1998 and 2013 were analyzed. One hundred and three (8.1%) patients had prostate cancer identified on final pathological prostatic tissue analysis. Average pre-HoLEP PSA was 7.2ng/mL (range: 0.04-121). Of note, two patients had pre-HoLEP PSA values higher than 65ng/mL in the benign group (120, 121 ng/mL). Both patients presented with retention and prostatitis prior to HoLEP. Average volume resected during HoLEP was 78.9 grams (SD: 53). The mean percent prostate tissue resected was 84%, which varied between 77% for the patients with prostate cancer and 85% among the non-malignant cases. Patients with prostate cancer identified on final pathological analysis were older, had higher pre-operative PSA, smaller pre-operative TRUS prostatic volume, and smaller HoLEP specimen weight (Table 1). Length of stay was similar between the two groups.

Prediction of prostate cancer

On univariate logistic regression analysis, age and pre-operative PSA were significantly associated with increased odds of identifying prostate cancer on final pathological analysis after HoLEP (Table 2). The weight of the HoLEP specimen was associated with decreased odds of prostate cancer identification in the HoLEP specimen (Table 2). On multivariate logistic regression, age, pre-operative PSA and decreasing specimen weight remained significantly associated with the presence of prostate cancer (Table 2). Figure 1 depicts the relationship between age and identification of prostate cancer when adjusting for pre-operative PSA and HoLEP specimen weight. Patients who were 80 years of age were at 20% predicted probability of having prostate cancer identified on HoLEP ($p < 0.001$).

Prediction of Gleason 7 or higher prostate cancer

Of the 103 patients with prostate cancer, 80 were Gleason 6 or less (78%), 14 were Gleason 7 (12 Gleason 3+4; 2 Gleason 4+3), and 9 were Gleason 8 or higher. Univariate regression results are shown in Table 3. On multivariate logistic regression, increasing pre-operative PSA was associated with increased odds of Gleason 7 or greater prostate cancer ($p = 0.002$) (Table 3).

Amongst the 103 patients identified with prostate cancer on HoLEP, follow-up information was available for 48. Thirty-five of 48 patients (73%) were followed with active surveillance and had received no treatment for their diagnosed prostate cancer at last follow-up. Twelve of the 48 patients (25%) underwent some form of primary therapy: 7 received external beam radiation, 3 underwent radical prostatectomy, and 2 received hormonal therapy. One patient with advanced disease underwent bilateral orchiectomy. A total of three patients from this cohort had developed metastatic prostate cancer. At last follow-up, three patients from the surveillance cohort had died of non-

prostate cancer related causes while two men with metastatic disease in the intervention cohort had died.

Discussion

Prior reports have identified the majority of prostate cancer in analyzed HoLEP tissue to be primarily low grade, indolent disease that has not required subsequent intervention. A recent study by Rivera et al suggested that more than 90% of patients found to have prostate cancer at the time of HoLEP were managed successfully with active surveillance¹³. Previous authors have reported a strong correlation between preoperative PSA and TRUS volume^{9,14}. Similar to simple prostatectomy for BPH, PSA values drop dramatically following HoLEP^{14,15} and subsequent increases in PSA-velocity are associated with increased risk of prostate malignancy⁹. The PSA kinetics of patients discovered to have prostate cancer after HoLEP have not been well studied, although it would be reasonable to hypothesize that increases in PSA in this patient population may represent disease progression as the primary PSA-producing transition zone has been completely eliminated. In our study, pre-operative PSA was the only variable associated with intermediate and high grade prostate cancer and it was significantly higher in the prostate cancer than benign cohorts. As demonstrated in Figure 1, men older than 70 years with smaller prostates were at the greatest risk of harboring prostate cancer and may warrant further workup prior to HoLEP.

A recent study by Zlotta et al found that 40% of men over 60 and nearly 60% of men over 80 had prostate cancer on autopsy specimen¹⁶. Over 40% of the prostate cancer identified in this older group was found in the transition zone which is the primary prostatic tissue removed during HoLEP¹⁶. These results contrast with our finding of only 8% incidental prostate cancer in our HoLEP patients. Despite this discordance, low rates of prostate cancer in HoLEP specimens was recently reported by Rivera et al who

cited a 13% cancer rate amongst their HoLEP patients¹³. Differences in comparison with historical autopsy series may be at least partially attributable to the vast majority of HoLEP patients having regular PSA checks or, in some cases, pre-operative prostate biopsies. Prior publications have suggested an association between BPH and prostate cancer that may be inflammatory mediated, even suggesting that the presence of BPH may increase the risk of malignancy¹⁷. In contrast, our results suggest a potentially protective effect of BPH and obstructive symptoms on the presence of prostate cancer. Whether this represents a true cause and effect phenomenon or merely isolating a pre-screened patient population remains unknown. In any event, future research exploring the relationship between BPH and prostate cancer should be considered.

It is well established that the risk of prostate cancer increases with age. Because BPH is the primary contributor to PSA rise and, as previously discussed, BPH may impact the incidence of prostate cancer, the relationship of prostate cancer in aging men with BPH is less understood. Despite the fact that we report a significant increase in the adjusted odds of prostate cancer detection for each decade of life over 60 (Figure 1), we did not find that there was an association between age and Gleason score. Although the relationship between age and prostate cancer was anticipated based on prior research, it does provide valuable support that the relationship between prostate cancer and age remains present even in men with co-existing BPH and obstructive symptoms, although it does not appear to impact the clinical significance of malignancy.

Unlike the positive association between age and the presence of prostate cancer, the relationship between prostate size and prostate cancer has previously been shown to be inverse¹⁸. Similar to prior findings, our cohort again demonstrated a decrease in the odds of prostate cancer identification as prostate gland size increased beyond 30g. Prior studies have hypothesized that the seemingly protective effect of larger glands harboring prostate cancer may be hormone mediated or related to a longer time before a

nodule penetrates the prostate capsule¹⁹. Additionally, pre-operative PSA, TRUS volume, and PSA density were all significant on univariate analysis. These findings suggest that prostate volume and PSA density may be important predictors of the presence of prostate cancer in men with BPH undergoing HoLEP and that these tests should be considered prior to surgery, particularly in men with higher risk of prostate cancer detection.

Although the limitations of PSA are well documented, PSA continues to be widely used as both a screening tool and a method of detecting prostate cancer recurrence^{20,21}. Our results suggest that there is value in obtaining a PSA pre-operatively for men with BPH who are scheduled to undergo HoLEP. All patients with an elevated PSA should be considered for prostate biopsy or repeat prostate biopsy before surgery. If localized prostate cancer is identified prior to HoLEP, some of these men may elect to pursue alternative procedures to address both BPH and prostate cancer concomitantly.

Predicting the biologic behavior of prostate cancer found at HoLEP remains challenging. As documented in the past on autopsy and whole mount tissue studies, typically only 20-40% of prostate cancer originates in the prostate transition zone^{16,22}. Therefore, our data may be under-representing the true incidence and volume of disease present and is in no way a perfect surrogate for predicting prostate cancer-related risk. Despite this, interpretation of our results does allow us to make relevant observations regarding prostate malignancy in patients with BPH undergoing complete transition zone enucleation: 1) HoLEP candidates who are older men with small glands are more likely to harbor cancer in their enucleated tissue. More specifically, independent of PSA and specimen weight, an estimated 20% of men who are at least 80 years old will have prostate cancer identified on HoLEP specimen; 2) the number of patients with prostate cancer in this cohort is low (less than 10%) with predominantly low grade disease; and 3) pre-operative PSA may be predictive of both presence and

aggressiveness of disease. Significantly, we have limited follow-up for our patients who were identified with prostate cancer on HoLEP as only 48 of the 103 continued to receive care at our institution. As we are a tertiary referral center, this is not unexpected; however, it does limit conclusions that can be drawn regarding the prognosis of patients diagnosed with prostate cancer from HoLEP specimen.

The majority of patients were outside referrals and cancer management was often directed by the referring provider and not captured in our database. For our internal HoLEP patient population diagnosed with prostate cancer, a general discussion of options was standard. Patients with low risk disease were recommended surveillance with a baseline PSA at six weeks followed by serial PSA checks and digital rectum exams every six months. Patients with a rising PSA or an abnormal exam were offered restaging TRUS biopsy and then treatment if indicated. Patients with intermediate and/or high risk disease post-HoLEP were staged appropriately and then offered definitive management, surgery vs radiation (external beam or IMRT) vs radiation and androgen deprivation typically without restaging biopsy.

Ultimately, the creation of a treatment and surveillance algorithm for managing this patient population based on numerous pre-operative variables is warranted. Similar treatment flowcharts for prostate cancer and non-HoLEP related BPH procedures are well documented²³. Future studies that evaluate PSA kinetics in patients with prostate cancer identified by HoLEP will aid in determining appropriate follow-up recommendations for this unique population. In our population of post-HoLEP patients with negative final prostate pathology, we anticipate PSA levels to fall below 1. If levels do not nadir below 1 or rise quickly in follow-up, we recommend repeat TRUS prostate biopsy as suspicion for prostate cancer is high. In the present study, our data offers potentially useful counseling data for patients prior to HoLEP regarding the risk of

prostate cancer being identified, as well as predicting higher risk disease in this patient population.

Our study has inherent limitations. It is retrospective and the number of prostate cancer patients is relatively low. Additionally, because a high percentage of our patients are referred from outside facilities, pre-operative TRUS techniques likely demonstrated inter-operator variability and TRUS volume was missing for a significant proportion of patients. Because 24% of TRUS volumes were missing, we used HoLEP specimen weight in all of our analyses. Additionally, TRUS biopsy was not standardized amongst referring physicians and this variable was not completely captured in our database. As a tertiary referral center, some post-HoLEP patients are lost to follow-up and therefore information on prostate cancer treatment initiation was not available for the entire cohort. It is possible that a disproportionate number of patients who required subsequent therapy received follow-up at our institution, thus creating a selection bias in the descriptive findings that we present. Despite the stated limitations, our study represents one of the largest analyzed cohorts of prostate cancer in HoLEP patients.

Conclusion

The existence of incidentally detected prostate cancer at the time of HoLEP in men with BPH and obstruction is low and the majority of patients will have low grade disease. Men over 70 with smaller glands are at the highest risk of harboring prostate cancer in their analyzed tissue. Optimal treatment and surveillance strategies for management of men with prostate cancer after HoLEP need to be established.

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List of Abbreviations

HoLEP	Holmium laser enucleation of the prostate
BPH	Benign prostatic hyperplasia
PSA	Prostate specific antigen
TRUS	Transrectal ultrasonography

Table 1: Holmium laser enucleation of the prostate: patient characteristics

	Benign	Malignant	p-value
N	1169	103	
Age (years), mean (SD)	70.0 (8)	74.5 (9)	<0.001
Pre-operative PSA (ng/ml), mean (range)	7.0 (0.04-121 ^a)	9.8 (0.13-61)	0.057
Pre-operative TRUS volume ^b (g), mean (range)	101.4 (9-391)	85.2 (23-231)	0.012
PSA density ^b , mean (range)	0.08 (0.0-1.3)	0.19 (0.0-6.6)	<0.001
Final specimen weight, n (%)			
<30g	191 (17)	29 (28)	0.005
30-100g	602 (53)	57 (55)	
100-150g	233 (21)	12 (12)	
>150g	105 (9)	5 (5)	
Percent prostate resected, mean (SD)	84.9 (41)	77.0 (29)	0.115
Length of stay (hours), mean (range)	29.3 (1-600)	33.8 (1-264)	0.233
6 month post-HoLEP PSA (ng/mL), mean (range)	1.2 (0.04-66)	4.5 (0.1-64)	<0.001

Abbreviations: SD, standard deviation; TRUS, transrectal ultrasound

p-value represents Pearson's chi-squared test or the Mann-Whitney test

^a Two patients in the benign group had pre-HoLEP PSAs higher than 65ng/mL. Both of these patients were admitted with retention and prostatitis.

^b TRUS volume not available for 24% of cases, PSA density not available for 25% of cases

Table 2: Logistic regression analyses of variables associated with prostate cancer

Univariate	Odds Ratio	95% CI	p-value
Age	1.07	1.04-1.10	<0.001
Pre-operative PSA	1.03	1.01-1.04	0.003
Pre-operative TRUS volume	0.99	0.99-1.00	0.012
Final weight of specimen			
<30g	REFERENCE		
30-100g	0.62	0.39-1.00	0.052
100-150g	0.34	0.17-0.68	0.002
>150g	0.31	0.12-0.83	0.020
Percent prostate resected	0.99	0.98-1.00	0.087
PSA density	4.40	0.67-28.81	0.122
Multivariate			
Age	1.07	1.04-1.10	<0.001
Pre-operative PSA	1.03	1.01-1.05	0.003
Final weight of specimen			
<30g	REFERENCE		
30-100g	0.53	0.33-0.87	0.015
100-150g	0.25	0.12-0.51	<0.001
>150g	0.17	0.06-0.48	0.001

Table 3: Variables associated with Gleason Score of 7 or higher in patients with prostate cancer

Univariate	Odds Ratio	95% CI	p-value
Age	1.03	0.97-1.09	0.318
Pre-operative PSA	1.08	1.03-1.14	0.001
Preoperative TRUS volume	1.00	0.98-1.01	0.810
Final weight of specimen			
<30g	REFERENCE		
30-100g	1.25	0.42-3.67	0.688
100-150g	0.77	0.13-4.47	0.768
>150g	0.96	0.09-10.23	0.972
Multivariate			
Age	1.01	0.95-1.08	0.661
Pre-operative PSA	1.08	1.03-1.14	0.002
Final weight of specimen			
<30g	REFERENCE		
30-100g	1.24	0.33-4.68	0.750
100-150g	0.78	0.11-5.51	0.805
>150g	0.41	0.03-6.10	0.521

